

The Cost of Cancer Treatment Study's Design and Methods

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*RAND Health
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PREFACE

Clinical cancer trials are supported by a combination of research sponsors, institutions, and third-party payers. However, it is unclear what additional costs—if any—are associated with treatment in a government-sponsored cancer trial. The National Cancer Institute, the National Institutes of Health, and the White House Office of Science and Technology Policy have a strong interest in estimating these costs so that informed policy decisions can be made about how to finance clinical trial research.

This report documents the design and methods of the Cost of Cancer Treatment Study (see www.costofcancer.org), a retrospective study designed to provide precise and generalizable estimates of the additional costs, if any, associated with clinical cancer research. Principal funding comes from the National Cancer Institute, with additional funding from the Office of the Director, National Institutes of Health, and from the National Science Foundation, as part of its support for the White House's Office of Science and Technology Policy. These offices as well as individuals in the cancer research community will be interested in this report on the design and methods of the study and the results of the study itself.

The study is being conducted jointly by RAND's Science and Technology Policy Institute and RAND Health. Originally created by Congress in 1991 as the Critical Technologies Institute and renamed in 1998, the Science and Technology Policy Institute is a federally funded research and development center sponsored by the National Science Foundation and managed by RAND. The institute's mission is to help improve public policy by conducting objective, indepen-

dent research and analysis on policy issues that involve science and technology.

RAND Health, the nation's largest private health-care research organization, has helped shape private- and public-sector responses to emerging health care issues for more than three decades. RAND Health's mission is to improve health care systems and advance understanding of how the organization and financing of care affect costs, quality, and access.

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SUMMARY

Traditionally, the cost of conducting cancer clinical trials has been supported by a combination of research sponsors, institutions, and third-party payers. However, health insurers and other payers are increasingly reluctant to reimburse for direct patient care provided as part of a clinical trial. These policies—driven in part by a perception that patients enrolled in trials incur substantial additional costs—might impede efforts to enroll patients in clinical trials. Yet there is little evidence regarding the costs of treating patients in clinical trials.

Given the great importance of timely clinical research, there is thus an urgent need for unbiased information on the possible effects of participation in government-sponsored clinical trials on patient care costs. Such data would make any cost-sharing burden explicit and could lead to better mechanisms for financing clinical trials.

This report documents the design and methods of the *Cost of Cancer Treatment Study* (CCTS), an ongoing effort to obtain precise and generalizable estimates of the direct care costs of patients who participate in National Cancer Institute-sponsored clinical cancer trials (see www.costofcancer.org). Using a retrospective design, the CCTS will sample multiple clinical trials and cancer providers around the country. Costs of treating patients in clinical trials at these providers will then be compared with a set of matched controls not in any trial, thereby yielding an estimate of the additional cost—if any—associated with clinical trial participation. Because of the large sample size

and the recruitment of patients in both academic and community settings, the CCTS will provide precise and generalizable estimates of these costs.

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We are deeply indebted to a distinguished group of advisors for helping us in the design and conduct of this study. They include Arnold L. Potosky, Richard Kaplan, Mary McCabe, and Joseph Lipscomb at the National Cancer Institute; Jane Weeks at the Dana-Farber Cancer Institute; Robert A. Figlin at the University of California, Los Angeles; and Joel Cohen at the Agency for Healthcare Research and Quality. This study also could not be conducted without the support of many people in the research community. These include Martin Brown, Susan Hubbard, Michael Montello, and Jeanette Sian at the National Cancer Institute; Judith Wagner at the Congressional Budget Office; John Crowley, Dana Sparks, and Jeanne-Marie Smith at the Southwestern Oncology Group; Sonja Hamilton at the North Central Cancer Treatment Group; Tom Malone and Rick Magnan at the Eastern Cooperative Oncology Group; Michael Maloney at the Cancer and Leukemia Group B; and Walter Cronin at the National Surgical Adjuvant Breast and Bowel Project; Nancee Relles and Eunice Little of University of California, Los Angeles; and Samuel Bozzette, Ronald Fricker, Kathryn Davis, and Deborah Rivera at RAND.

Nearly 8.5 million Americans who have had cancer are alive today. These individuals are living longer and experiencing a better quality of life than ever before, in part because of continuing advances in cancer care. Most of these advances stem from clinical research studies that rigorously test new ways of treating cancer or of reducing the side effects of existing treatments. For example, curative treatments for leukemias, lymphomas, and germ-cell tumors were developed as the result of clinical trials, and the longevity for people with breast and colorectal cancer has risen in recent years because of clinical trials that carefully evaluated the efficacy of new therapies [1,2]. Other clinical trials have helped establish better ways of caring for cancer patients, for example, using less-invasive surgical procedures and reducing negative side effects [3,4,5].

Traditionally, the cost of conducting cancer clinical trials has been supported by a combination of research sponsors, institutions, and third-party payers. However, health insurers and other payers are increasingly reluctant to reimburse for direct patient care provided as part of a clinical trial [6]. This reluctance—driven in part by a perception that patients enrolled in trials incur substantial additional costs—impedes efforts to enroll patients in clinical trials. Yet there is little evidence regarding the costs of treating patients in clinical trials.

Given the great importance of timely clinical research, there is thus an urgent need for unbiased information on the possible effects of participation in government-sponsored clinical trials on patient care

costs. Such data would make any cost-sharing burden explicit and could lead to better mechanisms for financing clinical trials.

In this report, we summarize current knowledge on the additional costs, if any, of treating cancer patients in clinical trials. We outline some methodological challenges facing any effort to generate precise and generalizable estimates of these costs. Finally, we introduce the Cost of Cancer Treatment Study (CCTS), an ongoing effort to obtain national estimates of the direct care costs of patients who participate in National Cancer Institute (NCI)-sponsored clinical cancer trials (see www.costofcancer.org).

One caveat should be noted at the outset. Clinical trials involve administrative and research costs beyond direct care, including staff training, trial administration, analysis, and reporting. All of these costs—which are underwritten by research sponsors such as NCI, institutions, or industry rather than insurers—are beyond the scope of this study. They clearly warrant further investigation.

The issue of payment for patient care costs is controversial. Most insurers or plans have policies that exclude coverage for services given as part of a clinical trial [7,8,9]. But since most payors do not track who is enrolling in clinical trials, and since most trials do not involve the use of expensive interventions, the usual cost of patient care for those enrolled in trials has typically been covered by health insurers. In practice, these policies are invoked for very expensive interventions, such as autologous bone marrow transplant (ABMT) and other experimental procedures, that, even when not associated with a clinical research trial, typically require special pre-approvals for coverage.

However, the past decade has witnessed enormous changes in health care delivery and financing, with much greater attention to the close management and accounting for all sources of costs. As a result, patients' participation in clinical trials has received increased scrutiny from insurers. While all parties unanimously agree about the importance of clinical research for improving the quality of patient care, there is no clear consensus as to how patient care associated with clinical research should be financed. In part, this reflects uncertainty about what the additional costs are, if any, from clinical trial participation.

Access to clinical trials has generated an enormous amount of attention from federal and state policymakers, as well as private organizations (mainly large health plans). All parties have identified the importance of precise, generalizable estimates of the additional treatment costs that may be attributable to participation in clinical

trials. There has been some regulatory action in the absence of such estimates,¹ and some plans have entered into voluntary agreements, most notably the recent agreement between the governor of New Jersey and a coalition of insurance companies that represents about 98 percent of the state's health care market to provide an estimated 25,000 cancer patients access to federally approved clinical trials. Nevertheless, without reliable cost estimates, it is difficult to assess the effects of these programs or to develop future policies.

Three recent studies have investigated the costs of care among cancer patients in single institutions or health plans and provide some useful evidence. Wagner et al. found that 61 cancer patients in Phase II and III cancer trials at the Mayo Clinic had at most 10 percent higher costs over a five-year period than a set of matched patients not enrolled in trials, although the difference was not statistically significant [10]. Fireman estimated that 135 patients in NCI-sponsored cancer trials at a large group model health maintenance organization (HMO) (Kaiser Permanente, Northern California) had approximately 10 percent higher costs over one year than 135 matched controls, with most of the difference attributable to chemotherapy administration costs [11]. Finally, Barlow estimated treatment costs over a two-year period among 77 patients in NCI-sponsored breast and colorectal cancer trials at another large HMO (Group Health Cooperative-Puget Sound) [12]. Compared with a general sample of non-trial patients in the same age range, time of diagnosis, and initial cancer stage, trial patients incurred slightly lower treatment costs, although the difference was not statistically significant; however, using data from 26 patients in breast cancer trials and matched controls, trial patients incurred 26 percent higher costs over a two year period.

These studies provide important evidence about the costs of care associated with trials. Nevertheless, more study may be warranted, for several reasons. First, existing studies have had sample sizes that

¹For example, NCI has entered into agreements with the Department of Defense and the Department of Veterans' Affairs to provide their beneficiaries coverage when participating in NCI-sponsored clinical trials; the Health Care Financing Administration is considering a demonstration project to make clinical trials available to all Medicare beneficiaries; and Virginia, Illinois, Maryland, and Rhode Island have enacted laws mandating at least partial coverage for participants in federally approved clinical trials.

were insufficient to detect cost differences that may be important for policy purposes—mainly because of the limited number of available trial patients at any single institution or health plan. Second, treatment patterns differ across institutions, and each of these studies was conducted within a single institution or health system. This makes the results difficult to generalize. Third, cases and controls matched at a single institution may differ in unobserved but important ways that affect treatment costs, as a result of self-selection into trials. Fourth, these studies excluded some potentially important dimensions of treatment. For instance, each study excluded treatment provided by clinicians outside the delivery system in which the respective study was conducted [10, 11, 12]; and one study excluded the costs of medications [10].

Finally, and perhaps most important, single institution studies may miss a significant phenomenon that affects costs—namely, that patients sometimes change institutions in order to participate in a clinical trial. If practice patterns and/or health care costs differ across types of institutions, which seems plausible, it might affect the estimates of the incremental cost of participation.

**OVERVIEW OF THE COST OF CANCER
TREATMENT STUDY**

Precise and generalizable estimates of the effects of trial participation on patient care costs could help policymakers refine mechanisms for financing clinical trials, with the goal of facilitating timely clinical research. Given the inherent limitations of single-institution studies, as discussed above, the most likely way to obtain such estimates is via a nationally representative sample of cancer patients enrolled in NCI-sponsored treatment trials, along with comparable control patients receiving treatment outside clinical trials. Only those data can answer the question, "How much more—if any—can insurers expect to pay if they permit their members blanket access to these trials, as opposed to access to only standard treatment?"

CCTS is designed to address the limitations of previous cost studies and provide these data. CCTS is a three-year study currently being conducted by RAND, with major support from NCI, the National Institutes of Health, and the National Science Foundation through the Office of Science and Technology Policy. Approximately 1,500 cancer patients will be recruited from a broad cross-section of trials and institutions nationwide. Ultimately, CCTS will yield a precise answer to the question above.

The CCTS uses a retrospective cohort design. Patients who were part of NCI-sponsored clinical trials during 1998 are being asked to participate in a study of their health care utilization approximately one year following their trial enrollment. Costs will be measured for all services used by this sample. Similar data will be collected for a comparable group of cancer patients not receiving care in a research

study who will serve as the “controls” for the CCTS. Efforts will be made to estimate the cost of care for a wide spectrum of services from all of a patient’s providers, using a combination of billing records, medical records, and an in-person survey questionnaire.

The choice of a retrospective design was a difficult one. In principle, a prospective design could substantially improve data quality relative to retrospective data collection, which is why such a design is preferred by studies such as the Medical Expenditure Panel Study [13]. However, prospective cost studies are expensive and difficult to implement when patients are accruing slowly and enrollment is taking place at hundreds of institutions. (This also partly explains why administration of clinical trials is so expensive.) Because of this expense—as well as the delay in getting results—the CCTS chose to follow other studies and use a retrospective design to assess costs [10, 11, 12]. Further details about the CCTS, and how it is designed to address previous limitations, are presented below.

SAMPLE DESIGN

An important goal of the CCTS is to assemble a representative sample of trial participants (cases) and matched controls who are cancer patients not enrolled in trials. After consulting with policymakers and insurance industry leaders, it was determined that the sample size should be sufficient to detect a 10 percent difference in costs for the results to be useful to policymakers. This dictated the target sample size of 750 cases and 750 controls, which allows us to detect a 10 percent difference with 80 percent power at a 0.05 confidence level. Detailed power calculations are given in Appendix A.

It was equally clear at the outset that the CCTS would not be feasible if it were necessary to approach hundreds of different providers and institutional review boards and collect records and data from huge numbers of sites. Otherwise, the costs of obtaining permissions from a multitude of study investigators and institutional review boards, and the effort needed to collect record data, would make the study prohibitively expensive.

The existence of timely national data on accrual from the “cooperative groups”—which are responsible for most of the clinical trial patient accrual on NCI-sponsored protocols—provided a convenient

sampling frame for a clustered, multistage design. Phase III patients were treated differently than Phase II patients because Phase II trials accrue patients at a much lower rate (Table 1), have higher mortality rates, and the national data on patient accrual were not as complete.

Phase III Patients

Using data of all active treatment Phase III trials supplied by the Cancer Therapy Evaluation Program (CTEP) at NCI, 35 trials were randomly sampled from the list with odds of selection proportional to actual patient accrual over a 6-month period. A list of all institutions affiliated with these 35 trials was compiled, from which 55 study sites were sampled randomly with odds again proportional to accrual. Because of the way data are reported, each study site consists of a core institution with numerous affiliates. The core institutions include a variety of providers in the cancer research community: Fourteen are NCI-designated Cancer Centers; 12 are Community Clinical Oncology Programs (CCOP), which include large oncology practices; and 29 are other institutions such as academic medical centers. The affiliates for each core institution are local hospitals and providers that accrue patients and report data to the core institution. There are about 250 such affiliates in the CCTS. On average, each CCTS study site participates in eight of the sampled Phase III trials and accrued 15 patients to these trials during the six-month period from October 1998 through March 1999. After selecting trials and associated institutions, all Phase III patients will be recruited. The projected CCTS sample of Phase III patients is described in Table 2.

Table 1
Number of Cooperative Group Trials and Patient Accrual, by Phase
(October 1998–March 1999)

| | Number of Trials | Number of Institutions | Total Patient Accrual | Median Accrual Per Trial |
|------------|------------------|------------------------|-----------------------|--------------------------|
| Phase II | 111 | 275 | 1,241 | 7 |
| Phase III | 92 | 643 | 3,316 | 25 |
| All trials | 203 | 686 | 4,557 | 16 |

SOURCES: NCI's Cancer Therapy Evaluation Program and cooperative groups.

Table 2
Characteristics of NCI Cooperative Group Phase III Trials and the CCTS Sample

| | All Phase III Trials ^a | | | CCTS Sample | | |
|-------------|-----------------------------------|---------|----------------------|---------------|---------|----------------------|
| | No. of Trials | Accrual | Percentage (rounded) | No. of Trials | Accrual | Percentage (rounded) |
| Type | | | | | | |
| Breast | 12 | 738 | 22% | 8 | 213 | 26% |
| Cervix | 3 | 194 | 6% | 2 | 49 | 6% |
| Colo-rectal | 9 | 498 | 15% | 6 | 160 | 20% |
| Glioma | 4 | 75 | 2% | 2 | 18 | 2% |
| Head & neck | 4 | 86 | 3% | 1 | 16 | 2% |
| Leukemia | 4 | 97 | 3% | 1 | 12 | 1% |
| Lung | 11 | 326 | 10% | 2 | 33 | 4% |
| Lymphoma | 5 | 116 | 3% | 2 | 26 | 3% |
| Other | 7 | 162 | 5% | 1 | 31 | 4% |
| Ovarian | 7 | 240 | 7% | 3 | 72 | 9% |
| Pancreas | 2 | 75 | 2% | 1 | 18 | 2% |
| Prostate | 5 | 321 | 10% | 2 | 37 | 5% |
| Uterine | 6 | 307 | 9% | 4 | 133 | 16% |
| Missing | 13 | 81 | 2% | 0 | 0 | 0% |
| Total | 92 | 3,316 | 100% | 35 | 818 | 100% |
| Region | | | | | | |
| Northeast | | 778 | 24% | | 150 | 18% |
| South | | 577 | 18% | | 202 | 25% |
| Midwest | | 919 | 30% | | 189 | 23% |
| West | | 787 | 23% | | 277 | 34% |
| Unknown | | 255 | 5% | | 0 | 0% |
| Total | | 3,316 | 100% | | 818 | 100% |

^aIncludes all Phase III cooperative group trials accruing at least one patient between September 30, 1998, and March 31, 1999.

Phase II Patients

Phase II trials accounted for 23 percent of accrual in NCI-sponsored cancer cooperative group trials in 1998. We expect a larger fraction at the NCI-designated cancer centers. To ensure that Phase II patients are adequately represented in the study, we will select them at the study sites identified in the Phase III institution sample. This selection will take place after institutional review board (IRB) approval is obtained, thereby ensuring timely information on accrual and reducing the number of deceased patients who are sampled.

Phase I Patients

Patients in Phase I trials (designed to evaluate dosage and toxicity) are excluded because so few accrue in each trial and expected mortality is very high, making it virtually impossible to recruit a representative sample. Information on Phase I accrual at our study sites will be collected; these data will allow us to conduct simulations to see how including Phase I trials might change our estimates.

SELECTING CONTROLS

Patients enrolled in one of our sampled trials are considered “cases” in CCTS. We also select a set of matched “controls.” These controls will be patients who meet the eligibility criteria of our trials, but who did not receive cancer therapy as part of any clinical trial. For each CCTS case enrolled in a particular trial at a particular affiliate or member institution, we will attempt to enroll one corresponding control at the same institution. However, when such a control is not available—e.g., because all such eligible patients are enrolled in the trial—we will seek a control with similar clinical characteristics at a different member institution.

Our definition of a control is less narrow than those employed by clinical trials. In a clinical trial, controls are selected on the basis of very detailed clinical criteria designed to ensure that any differences in outcomes cannot be attributed to underlying disease severity, but rather to the intervention under scrutiny. Such a strategy is not well-suited to the CCTS. It would require detailed abstraction of a very large number of medical records, a practice that is difficult to implement and prohibitively expensive, given the number of patients and providers. It also may be too stringent. For an analysis of costs, for example, we want to be able to include a control whose age fell just outside the eligible range of a clinical trial—and hence was not able to enroll in the trial—but otherwise had the clinical characteristics of trial participants.

Once a control has been enrolled in the CCTS, we will adjust for differences in case mix. Such a mixed strategy has been recommended for observational studies in which exact matching is logistically difficult [14] and in which there is concern that differences between cases and controls will remain even after matching on a specific number of

characteristics, since such differences may lead to biased estimates of the effects of interest and/or reduce model precision [14, 15]. The rest of this section provides detail on this strategy.

The instructions that we are providing to local study staff for identifying controls are included in Appendix B. Our first step will be to identify, at each institution, potential controls using logs of patients who were offered enrollment in our trials but who did not enroll. Second, we will use automated data sources at member institutions—particularly cancer registries—to generate lists of potential controls, using queries that identify patients based on each patient's age and gender, date of diagnosis/remission, cancer site, stage, and histology. RAND will provide technical support to facilitate these queries.

At locations where cancer registry data are unavailable, and at affiliates, we will ask local clinical staff to identify potential controls using a variety of sources: automated medical or billing data listing patients with particular clinical characteristics, medical record scans, and providers' memory. Where possible, we will rely on automated data to reduce the potential for bias in identifying controls. We will also use these methods to identify potential controls for trials in our sample that involve progressed or relapsed cancer, since cancer registry data are not well-suited for identifying such patients.

In each step, once potential controls have been generated, research staff at each institution will briefly screen the medical record of each potential control. To facilitate this brief screen, RAND is reviewing the protocol eligibility criteria of each sampled trial to prepare an abridged set of criteria; patients will be eligible as CCTS controls if they met abridged protocol entry criteria for the trial to which they are being matched. The abridged protocol entry criteria will focus on criteria likely to affect the course of treatment (and therefore medical costs), including stage, histology, and comorbid conditions. An expert panel of oncologists will identify these criteria using a Delphi method to review the protocols of all sampled trials.¹ Although they

¹For example, where the protocol entry criteria specifies that creatinine must be normal, the expert panel might recommend that patients with creatinine levels up to 1.5 times normal be considered as acceptable controls for CCTS; similarly, if the trial

will be significantly shorter than the full protocol entry criteria in order to expedite chart review, the abridged criteria will provide sufficient detail to match controls across a variety of important domains.²

RAND will use the abridged criteria to generate screening forms that allow research staff at each institution to identify eligible controls from brief medical record reviews. These forms are similar to those used by staff in the CCTS pilot study and are modeled after eligibility forms used by the cooperative groups.

Depending on the number of potential controls identified for each sampled trial, and their distribution across institutions, we will either seek to enroll every potential control or we will randomly sample a subset of them. For each case and each control who enrolls in the study, we will ask that they permit detailed abstraction of their medical records. To account for any remaining differences between cases and controls, we will account for patients' clinical and demographic characteristics—as well as information on whether they received care on or off protocol, and in member or affiliate institutions—in all our analyses of medical costs. Our multivariate methods are described in additional detail below.

INSTITUTION RECRUITMENT

Obtaining and maintaining the cooperation of sampled study sites are critical to the success of the study. CCTS procedures are designed to be minimally disruptive and to preserve confidentiality of patients and providers, and there will also be reimbursement for implementing these protocols. Study procedures for the CCTS were modeled after the HIV Cost and Service Utilization Study, a RAND study that collected data on approximately 3,000 HIV-positive patients from 120 providers nationwide [16].

specifies a white blood cell count of at least 3,000/mm³, the panel might recommend that levels of at least 2,500/mm³ be permitted among CCTS controls.

²To test this approach, RAND used cancer registry data at a large academic medical center to identify potential controls for four sample protocols (N=130 patients). We then abstracted the medical records of each potential control. Approximately 38.5 percent of potential patients met the complete protocol entry criteria for the trial to which they were being matched. Using abridged protocol entry criteria, 43.4 percent of patients matched.

Recruitment will work within the existing clinical trials infrastructure through the NCI cooperative group chairs and the study chairs; then permission to contact and recruit cancer patients will be obtained from local principal investigators (PIs) at each selected institution. Local PIs will be asked to identify a "site captain" to assist with procedural matters—typically a research nurse, a social worker, or an administrative assistant. The site captains will help navigate the IRB process, identify and recruit patients and controls, and collect data from medical and billing records.

The CCTS has already been approved by RAND's Human Subjects Protection Committee, and procedures have been designed with the participation of the national Office for Protection from Research Risks to allow institutions to participate without the necessity of an IRB review. However, many institutions will opt for review. RAND's experience with the HIV study suggests that the study protocol will ultimately be acceptable to most IRBs.

PATIENT RECRUITMENT

Eligible patients will initially be contacted by their own providers, who will obtain permission for RAND to contact the patient about the study. For patients, there are two dimensions of study participation: (1) completing a patient survey and (2) granting RAND permission to review their medical records and billing information from all named providers. Patients will be compensated for their time and will be informed that their participation in the CCTS is important in the scientific effort to foster the development and testing of new cancer therapies that will ultimately benefit all cancer patients.

DATA SOURCES

The data collection will obtain detailed cost and service utilization—and the factors that influence them—for the sample of cases and controls. Three types of data will be collected:

- Information obtained via the screening process to select controls (such as tumor registry data).

- A patient survey to identify all providers, collect utilization information, and ascertain insurance coverage, comorbidities, and sociodemographics.
- Medical and billing records from Health Care Finance Administration (HCFA) providers (both institutions and professionals) to ascertain more-detailed clinical characteristics, utilization, and costs.

The patient survey will be administered by telephone and will take approximately 35 minutes to complete. All patients will be asked to name all of the providers they have seen since a specified reference date, including providers of inpatient care, ambulatory care, home health care, and pharmacy services. For trial patients, the reference date is simply the date of trial enrollment. For controls, the reference date will be analogous clinical milestones, such as the date of diagnosis or date of relapse. The recall period for patients regarding their providers should average about one year, but it may extend up to 18 months.

Other patient characteristics known to affect the use of health care services will be identified, including demographics, insurance coverage, health status, and comorbidities. Questions about clinical trial participation and diversion of care to institutions offering trials will also be included. The survey will also ask about service utilization over the preceding 6-month period. Despite some concerns regarding recall of utilization (discussed later), these data can be used to provide some preliminary cost estimates, and they will also facilitate imputation of missing medical and billing data.

After the patient survey is completed, each respondent will also be asked to sign and return a permission form granting RAND access to billing and medical records for all providers identified by the respondent in the survey. Records will be reviewed and abstracted back to January 1998. This window extends beyond the period of survey recall since it is operationally easier to abstract records using a fixed calendar date, rather than the reference date for the survey, which varies with each patient depending on either trial enrollment or date of diagnosis or relapse.

MEASURING COSTS

For the CCTS, costs serve as a common metric for gauging the direct resources expended in providing care. Thus, costs are defined as a *dollar-denominated measure of resource utilization*. This definition is closely linked to other important financial concepts, including *charges*, *out-of-pocket expenses*, and *payments*. These will be measured as well, but they are not equivalent.

Four sources of data will be used to estimate costs: patient self-reported utilization from survey data, medical record data, billing record data, and standard sources on the prices of certain units of services. Two strategies for estimating costs will be used. In the first method, prices will be assigned to self-reported utilization and then summed across services to obtain costs. Prices will be assigned using a fixed set of prices, such as the Medicare Fee Schedule [17, 18] for physician services. This has obvious limitations, most notably the reliance on patient report for utilization over a 6-month period, but it will provide a preliminary estimate of costs prior to the availability of records data. The information thus obtained will be reported to NCI, but is not intended for use in publications. Results from this analysis will be used to identify unanticipated types of significant resource utilization and will provide a measure of cost differences due solely to differences in utilization.

In the second method, billing records from participating patients will be used to assign prices. When billing data cannot be obtained, service use can be imputed using utilization reports from medical records and the patient survey, and costs can then be estimated using prices as described above for the first method. For patients who are 65 or older (30–35 percent of CCTS patients), billing records will be obtained from HCFA. For other patients, RAND will engage an independent contractor to retrieve and abstract medical and/or billing records from health service providers. Billing records can be regarded as the most complete source of data on service utilization. Charges and payments listed in billing records will provide an alternate source of inputs for pricing models, with careful attention paid to the tenuous relationship between charges or cost-to-charge ratios and the economic costs of health services.

A substudy of the CCTS will use HCFA billing records linked to data in the Surveillance, Epidemiology, and End Results (SEER) database. This study will use data on health service utilization and payments made for those services to refine the prices assigned to services in the main study. This data will also allow the investigators to evaluate the precision and biases associated with methods currently used to estimate health service costs under conditions of incomplete data and censoring.

ANALYTIC APPROACH

The CCTS will assess differences in overall costs—not just costs for treating cancer—between cases and controls. Unlike the matched case-control method, multivariate regression models will be used for *ex post* regression adjustment on the matched samples [19, 20]. These will allow adjustment for covariates that were not exact-matched to further reduce potential bias when estimating cost differences between cases and controls. This joint approach—matching combined with regression adjustment—is preferable to matching alone in many instances [20].

The models will explain medical costs as a function of demographic characteristics, comorbid conditions, prior therapy, stage, histology, insurance status, and trial status (whether the patient is enrolled in a trial). More-complicated models that classify clinical trials according to a taxonomy that reflects possible cost differences will also be explored. The initial taxonomy will classify trials according to phase, adjuvant status, type of intervention, and whether they involve a control arm. Estimates of the coefficient for trial participation from these regressions will yield the cost differential—if any—associated with trials, as well as estimates of how this difference varies by trial and institution characteristics.

ESTIMATING COSTS ASSOCIATED WITH THE DIVERSION OF CARE

Patients reach clinical trials in a number of ways. In many cases, patients may seek out or be referred to a clinical trial being conducted at the institution where they are already receiving care. However, some patients may change providers in order to participate in a

clinical trial, for instance switching from a community provider to an academic medical center (or from a community provider that does not do clinical research to one that does). If practice patterns and/or health care costs differ across different types of institutions, as seems plausible, treatment costs for these patients will change as a result of this shift for reasons that are independent of trial participation *per se*.

Unfortunately, there is currently little empirical evidence on the extent to which patients shift across provider types to enroll in clinical trials, nor on the extent to which treatment costs for cancer care differ systematically across provider types. Because CCTS will be enrolling cases and controls receiving care in different types of institutions, we will be able to examine the possible scope of such effects. For example, we will measure costs for the subgroups shown in the following matrix:

| | Treated Primarily at Academic Medical Center | Treated Primarily by Community Provider |
|------------------------|---|--|
| Patients in trials | A | B |
| Controls not in trials | C | D |

Comparing groups A and C gives the incremental cost ($A - C$) of trial participation at academic medical centers. This can be compared with at least two important alternatives:

- $B - D$: The incremental cost of trial participation in community settings.
- $A - D$: The incremental cost of trial participation, assuming patients change providers from a community setting to an academic medical center to be on a trial.

The CCTS sample frame covers only institutions that are enrolling patients in NCI-sponsored treatment trials. This does include a large number and wide range of providers, including academic medical centers, smaller hospitals, community clinics, specialty providers such as radiation therapy centers, and small oncology practices. Nevertheless, presumably some cancer patients are treated by institutions outside our sample, and we will not be able to assess the costs of treatment in such settings.

POSSIBLE BIASES

Two Year Follow-Up

This study looks at costs one year following trial enrollment.³ Participation in a clinical trial may lead to better health outcomes and future cost savings outside that window. However, Wagner et al. [10] reported that, for a five year follow-up, the largest incremental difference in costs occurs within six months—a period easily captured in the CCTS design.

Selection Bias

Patients who were eligible for a trial but did not enroll may be systematically different in ways not observed from those who did enroll, and these differences may affect costs. This potential bias can be addressed in three ways. First, survey items will ask about patient preferences for care and the degree of self-reliance. Second, some controls will likely be enrolled who wanted to participate in a trial but were denied entry for “exogenous” reasons—e.g., the insurer refused to let them participate, or they were not eligible on narrow clinical grounds. Third, some controls will be drawn from institutions where the trial is not offered. By comparing these “exogenous” controls with other controls, the extent of this selection bias can be assessed.

Recall Bias

It is uncertain whether patients can accurately recall their providers over the past 18-month period and their utilization over a 6-month period. Most of the literature on self-reported health care looks at bias in recall of utilization and expenditure data. The major problem with self-reported utilization data is the net omission of medical events [21], a phenomenon experimental psychologists associate with the exponential decay of memory [22,23,24]. Fortunately, the omissions tend to be less salient—and less costly—events, with the recall of inpatient episodes better than outpatient care [25], and pa-

³Because of the timing of data collection activities, CCTS may obtain up to two years of data on some patients.

tients sometimes include utilization outside of the recall window—a process known as “telescoping” [26,27]. For this reason, the CCTS strategy to estimate final costs relies primarily on recall of providers from whom medical and billing records will be obtained. Memory clues will be used to facilitate patient recall [21,28]. Self-reported utilization—in conjunction with medical records—will be used for preliminary cost estimates and for improving the imputation of service use from providers who do not provide billing data.

Deceased Patients

A substantial minority of the sampled patients may have died before they can be contacted. Since the terminal phase of care is so costly [29], it would be inappropriate to exclude them. Therefore, medical and billing records data will be collected for cases and controls who have died following procedures established in conjunction with local IRBs. To assess the potential bias that might arise because of the higher rates of missing information among the deceased, stratified analyses will be conducted.

Nonresponse

Controls may be less likely to participate in our study than cases. To assess the degree of nonparticipation, and whether it might affect costs, we will ask participating providers to fill in some basic demographic and utilization data on all patients who decline to participate. A copy of the nonresponse form is contained in Appendix C.

Evidence suggests that employers and health plans are reluctant to pay for care delivered as part of a clinical trial. Such denials of coverage limit patient access to trials and could impede or bias clinical research. Unfortunately, these decisions are being made in the absence of accurate information about the cost of clinical trial participation. Preliminary estimates are available; but these come from small studies at only a few institutions. The Cost of Cancer Treatment Study is an ambitious effort to measure the incremental treatment cost of cancer trials and to address limitations of previous studies. Successful implementation is predicated on the participation and cooperation of the cancer community. If successful, the study will provide generalizable results that should be of great use to insurers, the cancer research community, and policymakers as they consider ways to finance clinical trial research.

A vibrant clinical research program is necessary to ensure continual improvements in the quality of patient care. However, with the current uncertainty about what the additional costs of clinical research are, it is difficult to achieve consensus on how they might be financed. The foregoing documents the design and methods of the Cost of Cancer Treatment Study in its efforts to provide such information on the costs of clinical research.

POWER CALCULATIONS

Cost data are to be collected on a sample of patients in clinical trials, and another sample not in clinical trials. These costs are assumed to have a log-normal distribution, based on past data collected and the requirements that the costs cannot be negative and the distributions are skewed to the right. It is desired to derive sample sizes to detect a given effect size and, conversely, given a sample size to determine the detectable effect.

It is possible to convert everything so the calculations can be done with normal distributions. Let $X = Y - \alpha$ where Y has a three parameter log-normal distribution, $Y \sim LN(\alpha\beta\sigma)$, with location parameter α , scale parameter β , and shape parameter σ . Then X has a two-parameter log-normal distribution, $X \sim LN(\beta\sigma)$, where with $\mu = \ln(\beta)$, and $Z = \ln(X) \sim N(\mu, \sigma^2)$. That is, each logarithmically transformed X has a normal distribution with mean μ and variance σ^2 . One immediate outcome of this result is that the calculated sample size is the same whether we use the original data or the logarithmically transformed data.

We usually generate a log-normal distribution by first generating each Z (for some μ and σ) and then exponentiating to get $X = e^Z$. This is the reverse problem, in that the moments of each log-normally distributed Y is given, and we desire to convert back to the Z to conduct the power calculations. To do this, consider the expressions for the moments for a three-parameter log-normal distribution:

$$E(Y) = \alpha + \beta e^{(\sigma^2/2)}, \text{ and}$$

$$\text{var}(Y) = \beta^2 e^{\sigma^2} (e^{\sigma^2} - 1)$$

If assumptions are made about the coefficient of variance and the location parameter, then these equations can be solved for the two-parameter log-normal random variable X to get μ and σ . For this application, based on similar data for Medicare cost of colorectal treatment, the following assumptions are made: The costs have a two-parameter log-normal distribution (i.e., location parameter $\alpha = 0$) and $CV_X = 1$, where CV_X is the coefficient of variance, defined to be the standard deviation of X divided by the mean of X . Thus, to find the value of σ iteratively, we solve following equality:

$$\sqrt{e^{2\sigma^2} - e^{\sigma^2}} = e^{\sigma^2/2},$$

β can then be calculated as $\beta = e^{\sigma^2/2}$, with the result that $\mu = \ln(\beta)$.

POWER GIVEN SAMPLE SIZE

We first consider the power to detect a given effect with a sample of 750 cases and 750 controls. The effect to detect the given effect is defined to be the percentage difference in costs between cases and controls. The hypotheses are $H_0: \mu = \ln(\beta)$ and $H_a: \mu > \ln(\beta)$. The p-value of the test is 0.05. The following table shows the power to detect various effects, given a range of CV_X .

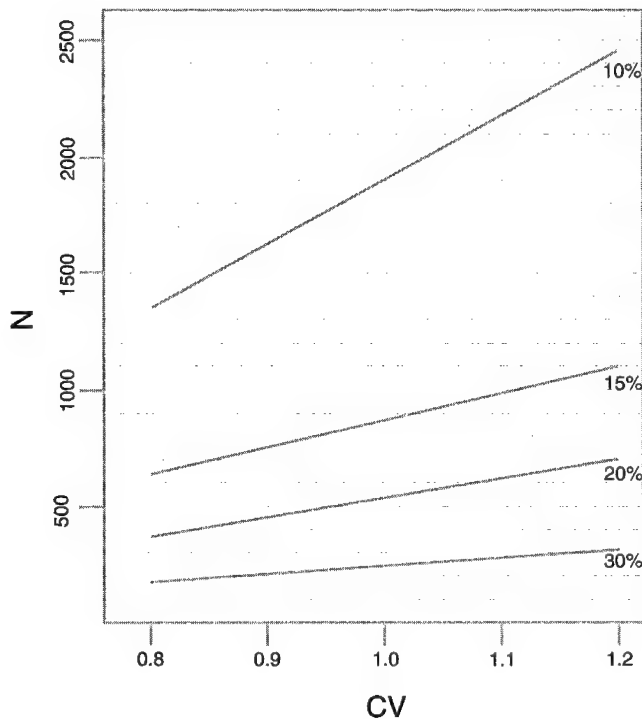
| Coef. of Variation (CV_X) | Power to detect a cost difference of | | | |
|-------------------------------------|---|-----|-----|-----|
| | 5% | 10% | 15% | 20% |
| 0.70 | 9 | 90 | 100 | 100 |
| 0.80 | 9 | 84 | 100 | 100 |
| 0.90 | 8 | 77 | 97 | 100 |
| 1.00 | 8 | 72 | 95 | 100 |

With a sample size of 750 cases and 750 controls, we can detect a 10 percent difference in costs with power of between 72 percent and 90 percent, depending on the coefficient of variation (CV_X). Preliminary data suggest that *unadjusted* costs have a CV_X of approximately 0.95. However, our analysis will include detailed covariates—including clinical status—that should be able to explain 15–20 percent of the variation in costs [30]. Thus, the relevant CV_X is probably in the range of 0.84 to 0.88. In addition, our estimates do not take into account the use of a case-control design, which should be more

powerful than random samples. Therefore, we conclude that this sample should be adequate to detect a 10 percent difference in costs with power of 80 percent.

SAMPLE SIZE NEEDED TO DETECT VARIOUS EFFECTS

Figure 1 shows the sample size needed to detect various effects for various values of CV_X . The relationship is linear. Each line represents the effect size.



NOTE: N refers to the combined sample sizes of both groups.

Figure 1—Change in the Sample Size for Various Coefficients of Variation (CV) for the Two-Sample Case

**INSTRUCTIONS FOR SELECTING AND CONTACTING
PATIENTS AT MEMBER INSTITUTIONS**

IDENTIFYING CASES

- 1) Identify all patients (including deceased patients) who enrolled in the selected trial at your institution between October 1, 1998, and December 31, 1999.

**IDENTIFYING CONTROLS VIA CANCER REGISTRY OR
OTHER DATABASES (PROTOCOLS THAT INCLUDE NEWLY
DIAGNOSED PATIENTS):**

- 1) Definition—

A “control” for this study is a patient meeting the eligibility criteria for one of the selected trials but who is not participating in that trial or any other clinical trial.

- 2) General Instructions—

For the trials we are studying, including trials on which you have enrolled cases (patients enrolled in the selected clinical trial) as well as all other trials in CCTS, we need to identify all controls who have received care at your institution since October 1, 1998.

- 3) RAND will help you work with the cancer registry (or other databases) at your institution to create a list of patients who may be potential controls. RAND will contact you to coordinate this activity.

- 4) Once a list of potential controls has been created, please review the medical record for each potential control using the abridged list of protocol entry criteria (provided by RAND) for the trial to which the control is being matched
- 5) Please keep RAND updated on the number of potential controls you have identified, and of the steps you have taken to identify controls, using the *Log for Control Patients* (provided by RAND).

IDENTIFYING CONTROLS (PROTOCOLS THAT INCLUDE PATIENTS WITH PROGRESSED/RELAPSED CANCER)

If your institution has enrolled cases in a protocol that includes progressed or relapsed ("nonanalytic") patients, please take the following additional steps:

- 1) Please review the abridged list of protocol entry criteria for each of these trials (provided by RAND).
- 2) For each case enrolled in these trials at your institution, please identify at least one patient who received care at your institution from October 1, 1998, through December 31, 1999, who
 - met the abridged protocol entry criteria for that trial at any time between October 1, 1998, and December 31, 1999
 - did not enroll in that trial, for whatever reason
 - has not participated in any clinical trial since October 1, 1998, to the best of your knowledge.
- 3) Where to look for potential controls:
 - Review the list of patients who were offered participation in the trial but who turned it down (if available);
 - Consult with the Principal Investigator for the selected trial(s) and his or her colleagues to see if he or she can remember any patients who may have been eligible for the trial but who were not offered the trial or who turned the trial down (for whatever reason); please review these patients' medical records to verify that they meet the protocol entry criteria for the selected trial.

- Periodically review the Principal Investigators' general patient lists to see if there are any patients who look eligible but who were not asked to participate in the trial (for whatever reason); please review these patients' medical records to verify that they meet the protocol entry criteria for the selected trial.
 - Scan medical records to identify potential controls.
- 4) Please keep RAND updated on the number of potential controls you have identified, and of the steps you have taken to identify controls, using the *Log for Control Patients* (provided by RAND).

CONTACTING CASES AND CONTROLS

- 1) For each case (patient enrolled in a selected trial), and each control identified using the steps above, send the patient a letter requesting permission to release their name, contact information, and basic background information to RAND.
- Print the patient contact letter provided by RAND on your own institutional letterhead and ask the patient's treating oncologist to sign the letter.
 - Record the patient's identification number, the date the letter was sent, and the enrollment status for that patient (agreed, refused, or pending) on the *Patient Enrollment Log* (provided by RAND). Please update and mail or fax this form to RAND every Friday.
 - Record the patient's name and telephone number(s) on the *Call Record Sheet* (provided by RAND) and record the outcome of every call you make to the patient on the call record. (Use this form to update the *Patient Enrollment Log*.)
- 2) Following up with Patients and Obtaining Consent

You must follow up with the patient by phone or in person to obtain verbal consent to release their name, contact information, and background information to RAND.

Ideally, phone follow-up with patients should take place no later than one week after the date the letter was mailed. Please use the *Script for Obtaining Permission for RAND to Contact Patients*

(provided by RAND) when calling patients. Please try to be as persuasive as possible and make it clear to the patient that you are only asking for permission to release their contact information and brief background information to RAND. Giving their permission for the release of this information does not commit them to participating in the study. They can make their final decision about participating in the study when RAND contacts them.

3) Transferring the Patient Screener and Nonresponse Form to RAND

Once you have obtained verbal (either by phone or in person) consent from the patient to release his or her contact and background information to RAND, please complete the *Patient Screener and Nonresponse Form* (provided by RAND) and fax or mail this form to RAND. Please note that you have to complete a separate form for each patient.

4) Procedures for Patients Who Refuse to be Contacted by RAND

If a patient refuses to give his or her permission to be contacted by RAND, please be sure to ask him or her for permission to release his or her background information to RAND anonymously. This information is very important and will allow RAND to generally describe those patients who chose not to participate in the study. Complete the appropriate sections of the *Patient Screener and Nonresponse Form* and fax or mail this form to RAND.

5) Procedures for Patients Who Are Deceased

Some patients selected as eligible for the study will be deceased either at the time of selection or may have died between the time they were selected and the time of enrollment. Please complete the appropriate sections of the *Patient Screener and Nonresponse Form* and mail or fax this to RAND. In addition, please request a copy of the patient's medical and billing records going back to January 1998 and send it to RAND (provided your institution allows you to do so).

6) Procedures for Patients You Are Unable to Locate

If after you have made a reasonable effort to locate a patient (for example, you have called information and you have looked in the

patient's medical record to see if they have an alternate address or telephone number) you are still not able to locate a patient, note this on the *Patient Enrollment Log*. Please complete the appropriate sections of the *Patient Screener and Nonresponse Form* and mail or fax this to RAND. In addition, please request a copy of the patient's medical and billing records going back to January 1998 and send it to RAND (provided your institution allows you to do so).

PAYMENT FOR IDENTIFYING AND CONTACTING PATIENTS

Please remember that you will be paid for identifying and recruiting patients for the *Cost of Cancer Treatment Study*. Each site will receive a minimum of \$250 initially and \$50 for each patient they identify and attempt to recruit for the study at the end of the recruitment period.

PATIENT SCREENER/NONRESPONSE FORM

Study Site: _____ Completed by: _____

PART ONE: PATIENT SCREENER

1. Is this patient a case or a control (as defined by the CCTS)?

(Circle One)

Case 1 —> CONTINUE

Control..... 2 —> GO TO QUESTION 3

2. If Case:

What trial is the patient enrolled in?

Trial ID #: _____

3. If Control:

For which trial(s) is the patient being matched as a control?

Trial ID #: _____

4. Did the patient agree to let RAND contact them about the study?

(Circle One)

Yes 1 —> CONTINUE

No 2 —> GO TO QUESTION 7,
SECTION THREE

PART TWO: PATIENT CONTACT INFORMATION

5. Sampled Patient Medical Record Number or Patient ID:

6. a. Patient Name: _____
First Middle Last

b. Street Address: _____

c. City: _____ d. State: _____ e. Zip Code: _____

f. Phone Number: Home: (____)____-_____

g. Work: (____)____-_____

PART THREE: PATIENT BACKGROUND INFORMATION

7. If the patient does not want RAND to contact them, will they allow the release of anonymous background information to RAND?

(Circle One)

Yes 1 —> CONTINUE

No 2 —> GO TO QUESTION 13

8. What is the patient's gender?

(Circle One)

Male 1

Female 2

9. What is the patient's date of birth? ____/____/____
MO DAY YR

10. What main racial or ethnic group does the patient belong to?

(Circle One)

White, not Hispanic 1

African American 2

Hispanic 3

Other/Unknown 4

11. What type of cancer does the patient have and what was the stage at diagnosis?

(Circle All That Apply and Write in Stage at Diagnosis)

- | | | |
|-----------------------|----|-------|
| Lung | 1 | _____ |
| Prostate | 2 | _____ |
| Colon..... | 3 | _____ |
| Rectal | 4 | _____ |
| Colorectal | 5 | _____ |
| Leukemia | 6 | _____ |
| Lymphoma | 7 | _____ |
| Breast | 8 | _____ |
| Ovarian | 9 | _____ |
| Cervix | 10 | _____ |
| Endometrium..... | 11 | _____ |
| Uterus | 12 | _____ |
| Melanoma | 13 | _____ |
| Glioma | 14 | _____ |
| Other (specify) | 15 | _____ |

PLEASE MAIL OR FAX THIS FORM TO:
KATHRYN DAVIS
RAND
1700 Main St.
Santa Monica, CA 90407
Tel: (310) 393-0411, ext. 7267 Fax: (310) 451-6921

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The Cost of Cancer Treatment Study

Traditionally, the cost of conducting cancer clinical trials has been supported by a combination of research sponsors, institutions, and third-party payers. However, health insurers and other payers are increasingly reluctant to reimburse for direct patient care provided as part of a clinical trial. These policies—driven in part by a perception that patients enrolled in trials incur substantial additional costs—might impede efforts to enroll patients in clinical trials. Yet there is little evidence regarding the costs of treating patients in clinical trials.

Given the great importance of timely clinical research, there is thus an urgent need for unbiased information on the possible effects of participation in government-sponsored clinical trials on patient care costs. Such data would make any cost-sharing burden explicit and could lead to better mechanisms for financing clinical trials.

This report documents the design and methods of the Cost of Cancer Treatment Study (CCTS), an ongoing effort to obtain precise and generalizable estimates of the direct care costs of patients who participate in National Cancer Institute-sponsored clinical cancer trials (see www.costofcancer.org). Using a retrospective design, the CCTS will sample multiple clinical trials and cancer providers around the country. Costs of treating patients in clinical trials at these providers will then be compared with a set of matched controls not in any trial, thereby yielding an estimate of the additional cost—if any—associated with clinical trial participation. Because of the large sample size and the recruitment of patients in both academic and community settings, the CCTS will provide precise and generalizable estimates of these costs.

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